Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting information

(New Journal of Chemistry)

First biocatalytic synthesis of piperidine derivatives via immobilized lipase catalyzed multicomponent reaction

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Table of Contents:

General procedures

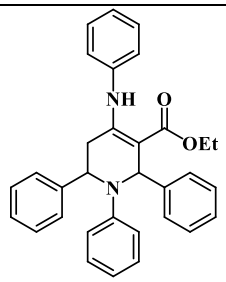
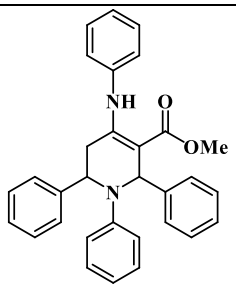
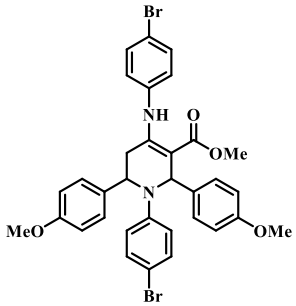
Reaction scale-up and catalyst reusability procedure: A mixture of ethyl acetoacetate (3a) (1.0 g, 1.0 equiv.), aromatic aniline (2a) (1.401g, 0.01536mmol, 2.0 equiv.), CALB@MHNTs (1.0 g), and ethanol (15 mL) as a solvent were stirred for 20 minutes in a round bottom flask at 55°C. Then benzaldehyde (1a) (1.56g, 0.01536 mmol, 2.0 equiv) was added to the reaction mixture and stirred for overnight. Upon completion of the reaction, the catalyst was separated from the reaction mixture using an external magnet and the product mixture was decanted off. The solid product obtained was then washed with ~20 mL EtOH (3-4 times) to further purify the product. The separated catalyst was reused in next catalytic cycle using the aforementioned protocol.

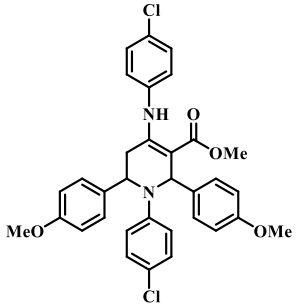
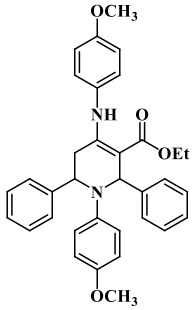
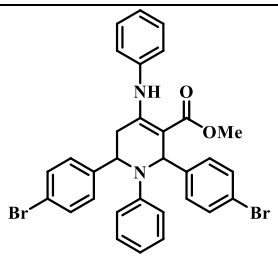
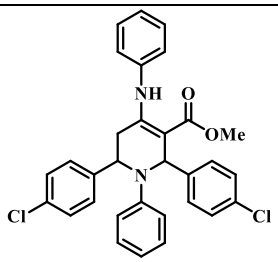
Procedure to find enzyme loading over functionalized magnetic support: The amount of lipase adsorbed on magnetic support was estimated using Bradford assay using BSA as standard.[1]

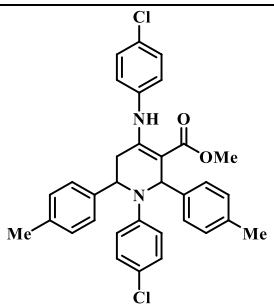
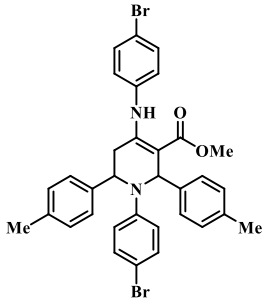
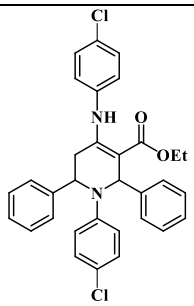
$$q = \frac{(C_i - C_f)V}{W}\left(\frac{mg}{g}\right)$$

Where q = amount of protein loaded over magnetic support (mg/g), Ci = initial concentration of protein in original solution before immobilization (mg/ml), Cf = final concentration of protein in supernatant after immobilization (mg/ml), V= volume of buffer added during immobilization (ml), W = weight of magnetic support (g). All the readings are recorded in triplicate and then averaged to find the amount of protein load on magnetic support.

Characterization of compounds:

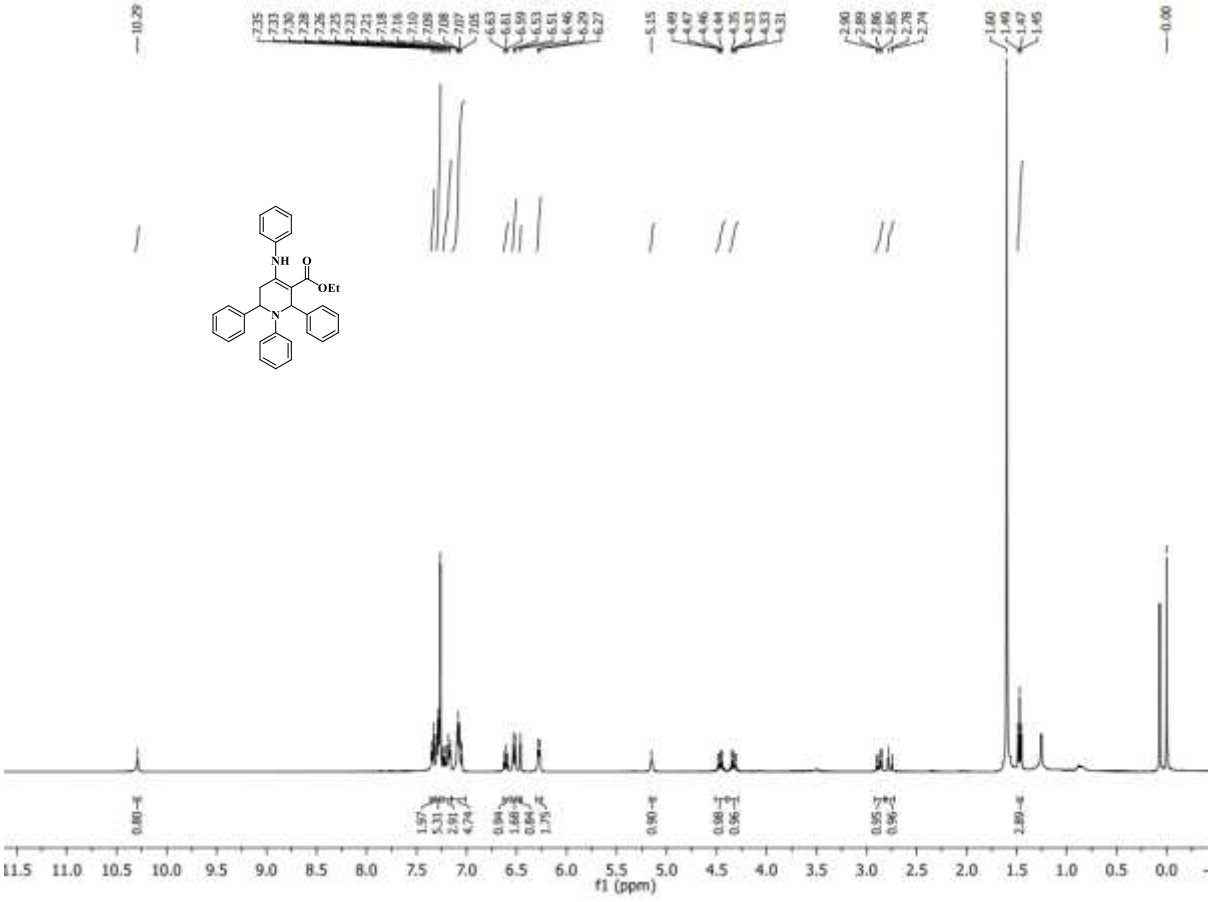
S.No.	Derivatives	H^1NMR Spectra	Ref.
1.	 **(4a) Ethyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate**	Yield= 90%, H^1NMR (400 MHz, $CDCl_3$) δ: 1.47 (t, *J*=7.1, 3H), 2.76 (d, *J*=16.0, 1H), 2.87 (dd, *J*=16.0, 4.0, 1H), 4.31–4.35 (q, 1H), 4.44 – 4.49 (q, 1H), 5.15 (br s, 1H), 6.28 (d, *J*=8.0, 2H), 6.46 (s, 1H), 6.52 (d, J=8.0, 2H), 6.59–6.63 (m, 1H), 7.05 –7.10 (m, 5H), 7.09-7.35 (m,10H) 10.29 (br s, 1H).	[2]
2.	 **(4b) Methyl-1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate**	Yield = 84%, H^1NMR (500 MHz, $CDCl_3$) δ: 2.74-2.79 (d, *J*=15 Hz, 1H), 2.84-2.89 (dd, *J*=15, 6 Hz, 1H), 3.93 (s, 3H), 5.14 (br s, 1H), 6.28 (d, *J*=7.6 Hz, 2H), 6.44 (s, 1H), 6.51-6.53 (d, *J* = 8.0 Hz, 2H), 6.59-6.61 (t, *J*=7.0 Hz, 1H), 7.04-7.31(m, 15H), 10.25 (s, 1H).	[2]
3.	 **(4c) Methyl-1-(4-bromophenyl)-4-((4-bromophenyl) amino)-2,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate**	Yield= 80 %, ^{1}H NMR (500 MHz, CDCl3) δ: 2.69 (d, *J*=12.4, 1H), 2.83 (dd, *J*=13.0, 6.4, 1H), 3.78, 3.91, 3.92 (3s, 9H), 5.02 (br s, 1H), 6.19 (d, *J*=8.5, 2H), 6.27 (s, 1H) 6.37 (d, *J*=9 Hz, 2H), 6.80-6.82 (m ,4H) 7.03(d, *J*=8.5 ,2H), 7.11-7.22 (m, 4H), 7.23 (m, 2H), 10.19 (br s, 1H).	[3]

4.	 **(4d) Methyl-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate**	Yield= 79%, ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.68-2.71 (m, 1H), 2.81-2.84 (m, 1H), 3.78 (s, 6H), 3.92 (s, 3H), 5.03 (br s,1H), 6.20-6.38 (m, 5H), 6.80-6.81 (m, 3H), 7.12-7.26 (m,9H), 10.20 (s, 1H).	[3]
5.	 **(4e) Ethyl-1-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate**	Yield= 65%, ^{1}H NMR (500 MHz, $CDCl_3$): δ: 1.40–1.43 (t, *J* = 7.5 Hz, 3H), 2.62 (dd, *J* =15.0 , 2.5 Hz, 1H), 2.76 (dd, *J* =15.5, 5.5 Hz, 1H), 3.65 (s, 3H), 3.73 (s, 3H), 4.25–4.32 (m, 1H), 4.37–4.42 (m, 1H), 5.03 (br s, 1H), 6.23–6.24 (d, *J* = 8.5 Hz, 2H), 6.32 (s, 1H), 6.45– 6.46 (d, *J* = 8.5 Hz, 2H), 6.60–6.65 (m, 4H), 7.16–7.31 (m, 10H), 10.14 (s, 1H).	[4]
6.	 **(4f) Methyl-2,6-bis(4-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate**	Yield= 82%,^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.73 (dd, *J*=15.0, 2.5, 1H), 2.81 (dd, *J*=15.0, 5.5, 1H), 3.91 (s, 3H), 5.06 (br s,1H), 6.32 (s, 1H), 6.40 (d, *J*=7.0, 1H), 6.45 (d, *J*=8.5, 2H), 6.64 (t, *J*=7.3, 1H), 7.0 (d, *J* =8.5 Hz, 2H), 7.05-7.17 (m, 7H), 7.37-7.39 (m, 4H), 10.23 (s, 1H).	[5]
7.	 **(4g) Methyl-2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate**	Yield= 76%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.74 (dd, *J*=15.0, 2.5, 1H), 2.82 (dd, *J*=15.0, 5.5, 1H), 3.91 (s, 3H), 5.07 (br s, 1H), 6.32 (s, 1H), 6.41 (d, *J*=7.0, 2H), 6.45 (d, *J*=8.5, 2H), 6.65 (t, *J*=7.3, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 7.06-7.18 (m, 7H), 7.37-7.40 (m, 4H), 10.23 (s, 1H).	[6]

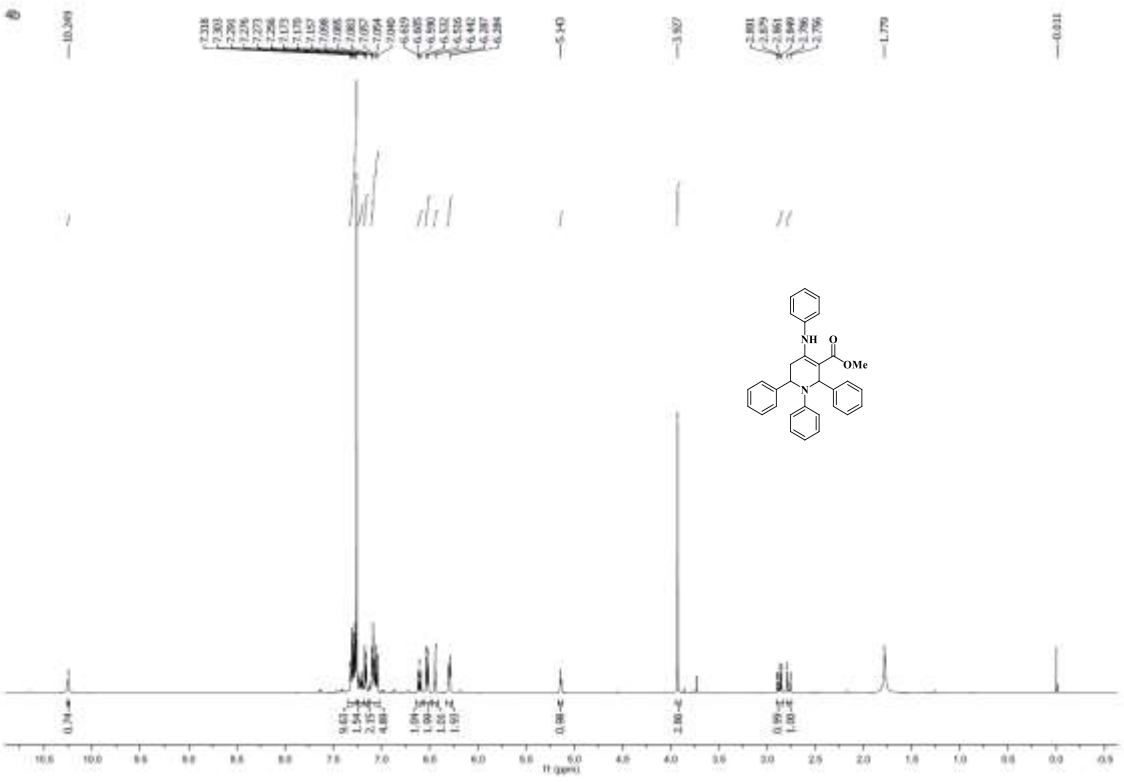
8.	 **(4h) Methyl-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-di-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate**	Yield= 78%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 2.34 (s, 3H), 2.66-2.70 (m, 1H), 2.81-2.86 (m, 1H), 3.92 (s, 3H), 5.05 (br s, 1H), 6.19 (d, *J* = 10.5 Hz, 2H), 6.31 (s, 1H), 6.40 (d, *J* = 11.0 Hz, 2H), 6.60 (d, *J*=8.5,1H) 7.01-7.14 (m, 12H), 10.18 (s, 1H).	[5]
9.	 **(4i) Methyl-1-(4-bromophenyl)-4-((4-bromophenyl) amino)-2,6-di-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate**	Yield = 71%, H^{1}NMR (500 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 2.34 (s, 3H), 2.64 (d, *J*=17.5, 1H), 2.84 (dd, *J*=19.0, 7.5, 1H), 3.93 (s, 3H), 5.06 (d, *J*=6.5, 1H), 6.12 (d, *J*= 10.0, 2H), 6.31 (s, 1H), 6.38 (d, *J*=11.0, 2H), 7.02 (d, *J=10.0*, 2H), 7.09(d, *J*=9.0,2H), 7.14 (d, *J*=15.0, 2H), 7.20 (d, *J=10.5*, 2H), 7.26 (s, 2H), 10.19 (s, 1H).	[6]
10.	 **(4k) Ethyl-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate**	Yield = 82%,^{1}H NMR (500 MHz, $CDCl_3$) δ:1.47 (t, *J* = 7.0 Hz, 3H), 2.70 (dd, *J* = 15.5, 2.0 Hz, 1H), 2.85 (dd, *J* = 15.0, 6.0 Hz, 1H), 4.31–4.35 (dq, *J* = 7.1,3.7 Hz, 2H), 5.11 (br s, 1H), 6.1 (d, *J*= 7.0, 2H), 6.38 (s, 1H), 6.42 (d, *J*=9.0, 2H) 6.96 (d, *J*=9.5, 2H) 7.04 (d, *J*=7.0, 2H), 7.14 (d, *J*= 6.0, 2H), 7.22-7.29 (m, 8H), 10.29 (br s, 1H).	[3]

Copy of 1H-NMR Spectra of polyfunctionalized piperidines.

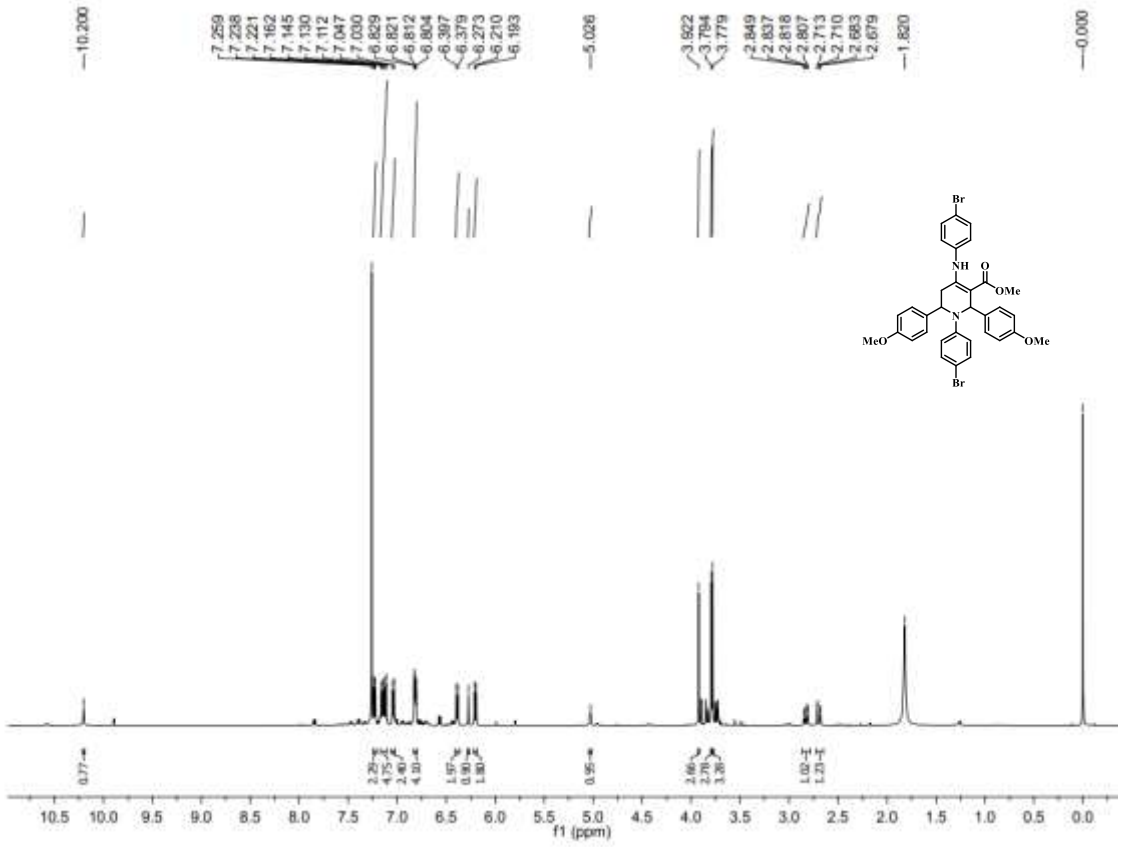
(4a) Ethyl-1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate



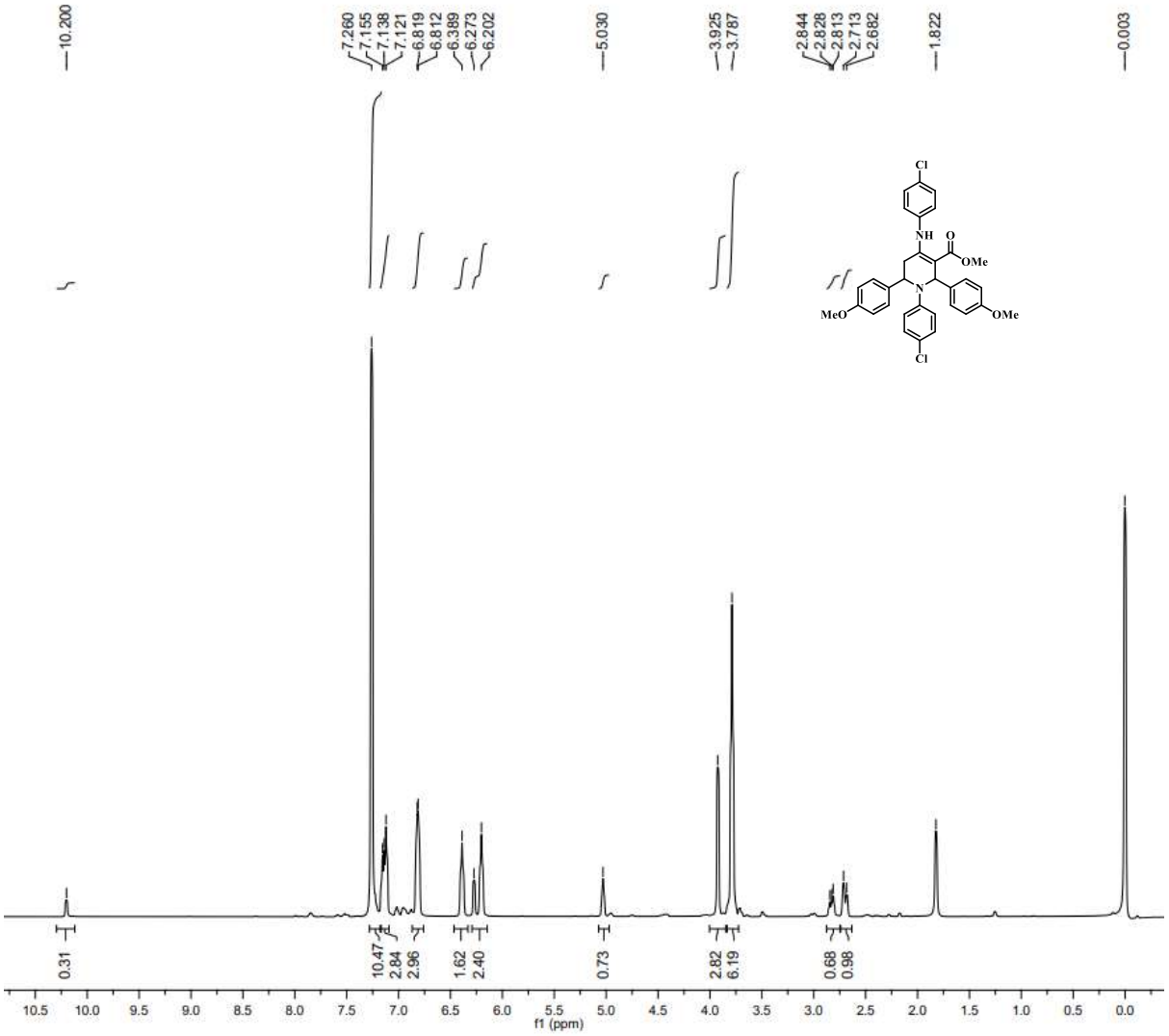
(4b) Methyl-1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate



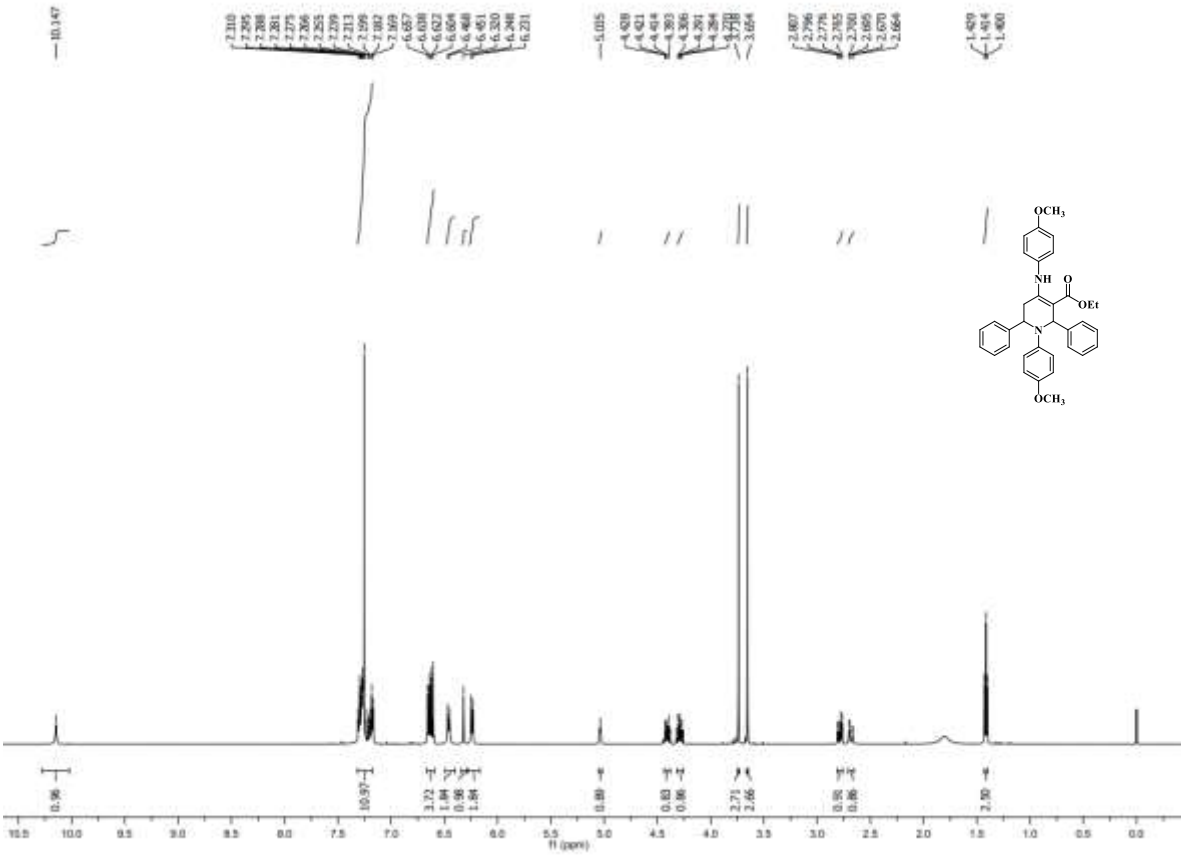
(4c) Methyl-1-(4-bromophenyl)-4-((4-bromophenyl) amino)-2,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate



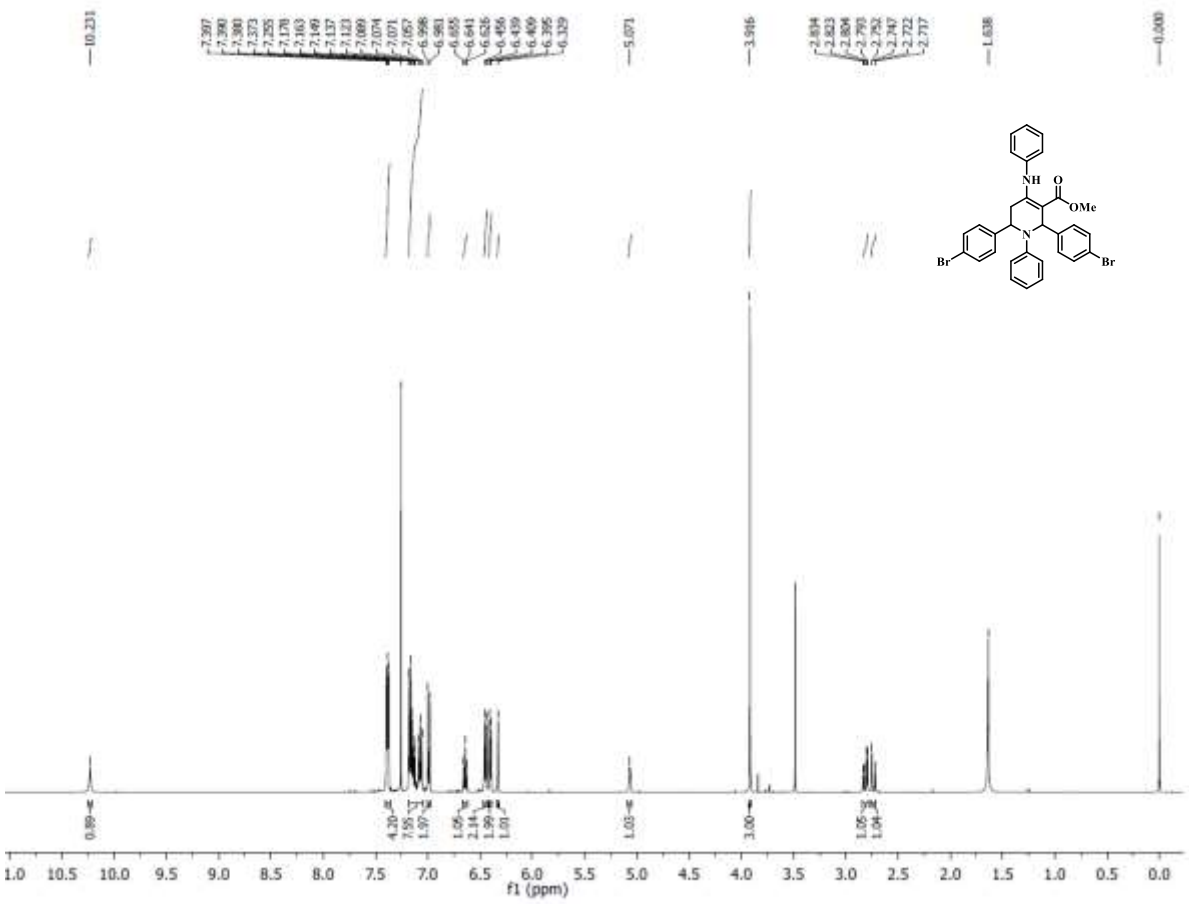
(4d) Methyl-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate



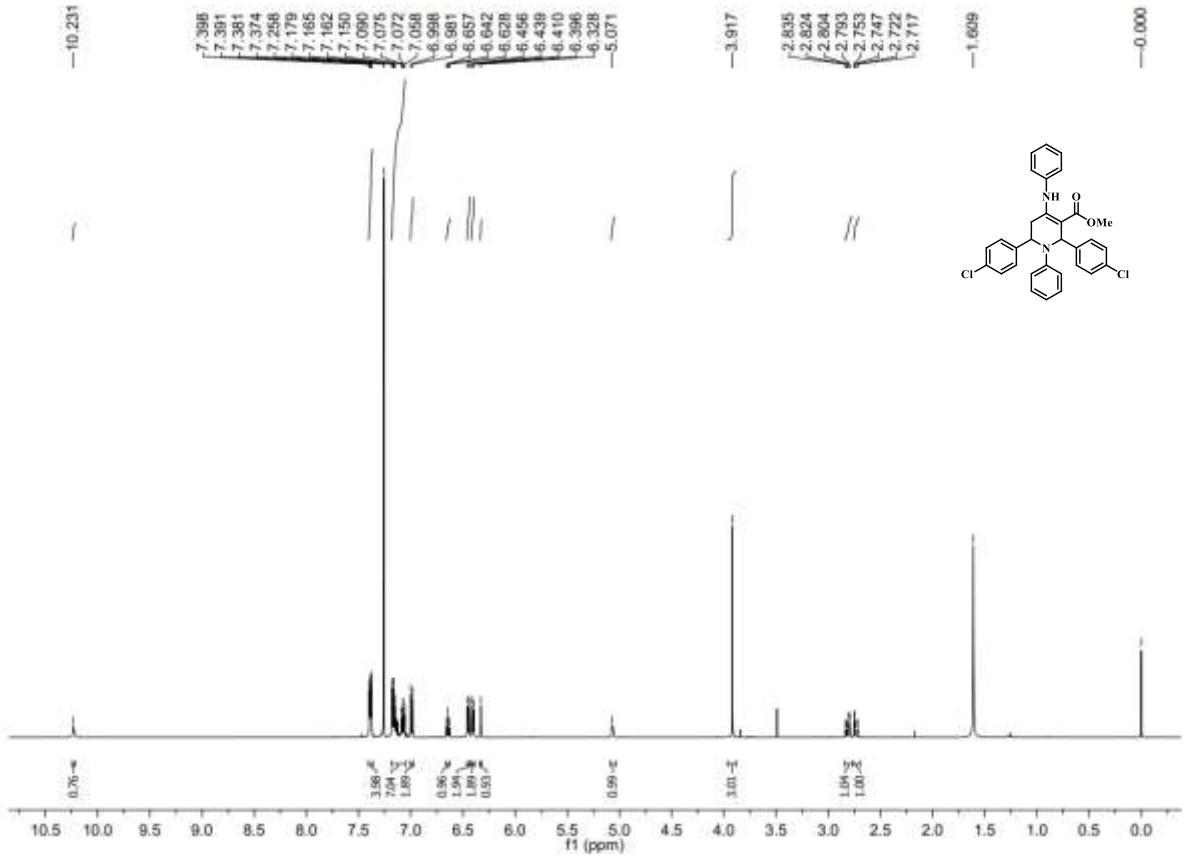
(4e) Ethyl-1-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate



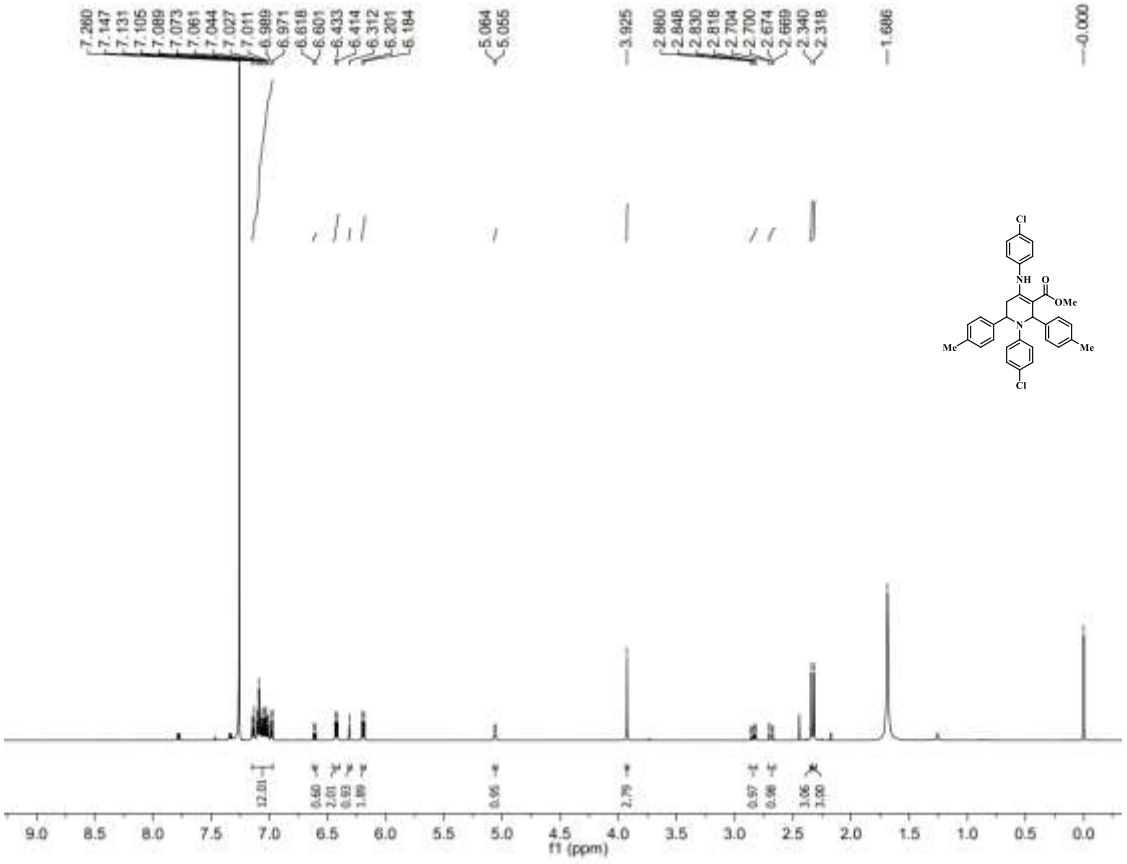
(4f) Methyl-2,6-bis(4-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate


10.231
7.397
7.390
7.380
7.373
7.255
7.176
7.163
7.149
7.137
7.123
7.089
7.074
7.071
7.057
6.998
6.981
6.655
6.641
6.626
6.456
6.439
6.409
6.395
6.329
5.071
3.916
2.834
2.823
2.804
2.793
2.752
2.747
2.722
2.717
1.638
0.000
NH
O
OMe
N
Br
Br
0.89
4.20
7.95
1.97
1.05
2.14
1.99
1.01
1.03
3.00
1.05
1.04
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

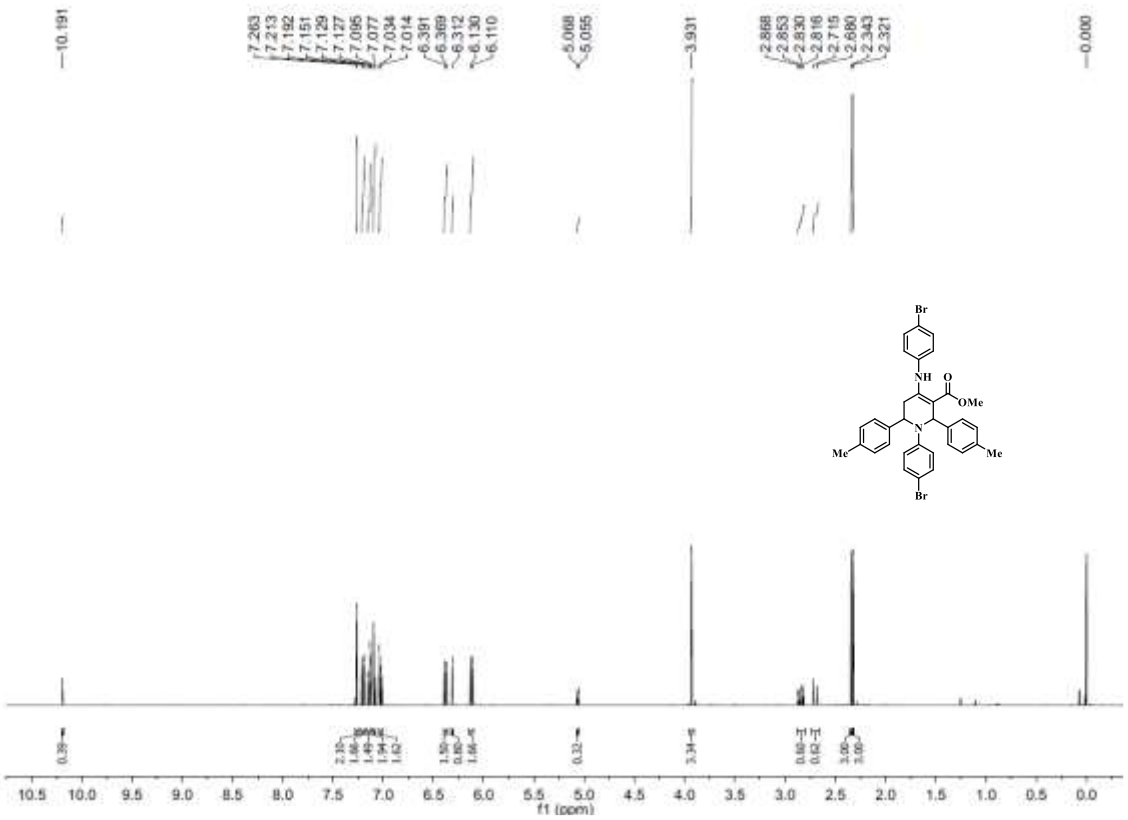
(4g) Methyl-2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate



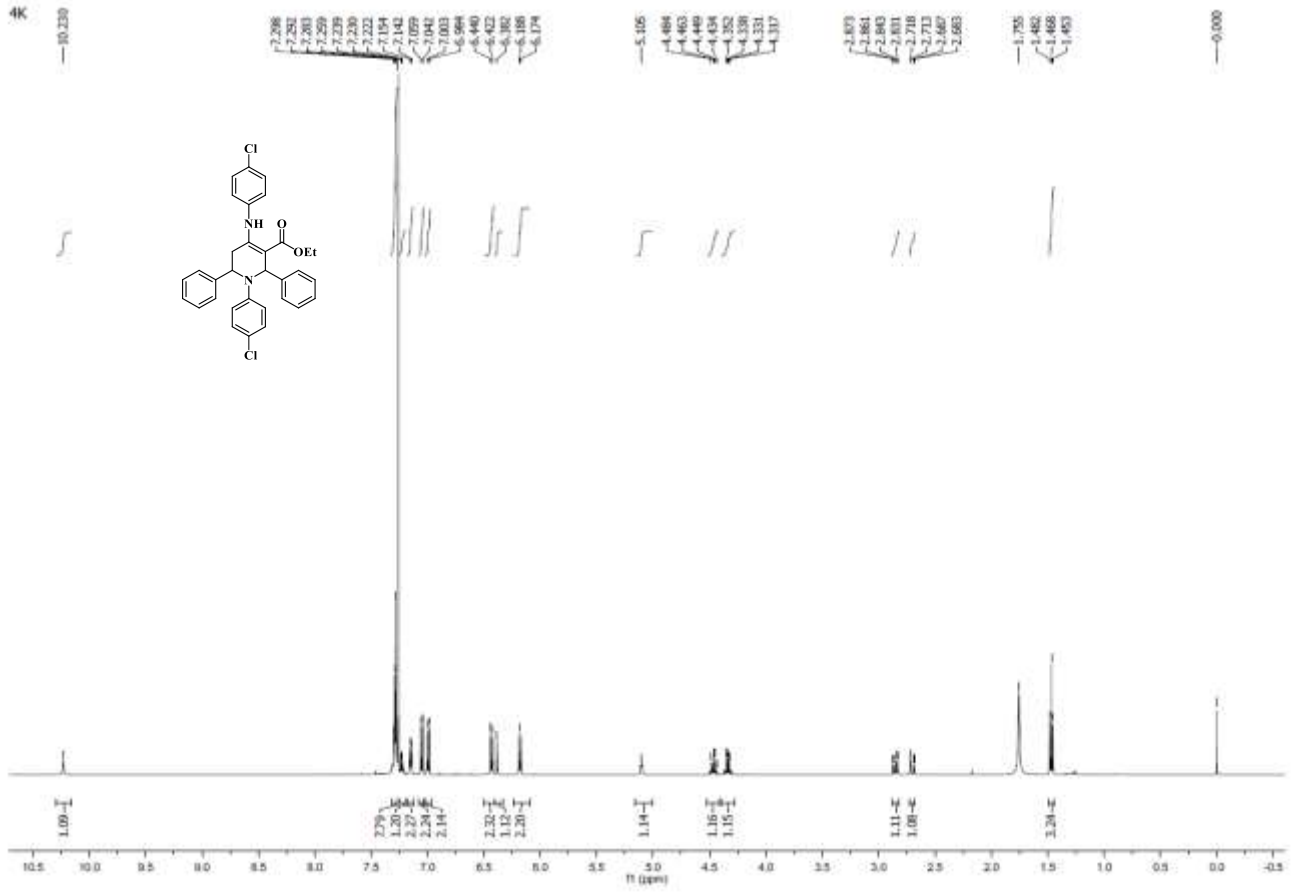
(4h) Methyl-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-di-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate



(4i) Methyl-1-(4-bromophenyl)-4-((4-bromophenyl) amino)-2,6-di-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylat



(4k) Ethyl-1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate



References

[1] a) M. M. Bradford Analytical biochemistry, **1976**, 76, 248-254; b) R. Baharfar, S. Mohajer, Catal. Letters **2016**, 146, 1729–1742.

[2] S. T. Fardood, A. Ramazani, **2018**, 12, 92-102.

[3] F. Mohamadpour, Polycycl. Aromat. Compd. **2020**, 40, 681–692.

[4] M. Misra, S. K. Pandey, V. P. Pandey, J. Pandey, R. Tripathi, R. P. Tripathi, Bioorganic Med. Chem. **2009**, 17, 625–633.

[5] B. Umamahesh, V. Sathesh, G. Ramachandran, M. Sathishkumar, K. Sathiyanarayanan, Catal. Letters **2012**, 142, 895–900.

[6] A. T. Khan, T. Parvin, L. H. Choudhury, J. Org. Chem. **2008**, 73, 8398–8402.